

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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In re Application of:  
Valerie Legrand et al.

Application No.: 10/826,690

Confirmation No.: 9585

Filed: April 19, 2004

Art Unit: 1618

For: MICROPARTICULATE ORAL GALENICAL  
FORM FOR THE DELAYED AND  
CONTROLLED RELEASE OF  
PHARMACEUTICAL ACTIVE PRINCIPLES

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Examiner: L. Schlientz

**DECLARATION OF CATHERINE CASTAN**

1. My name is Catherine CASTAN.
2. I have been an employee of Flamel Technologies, S.A. since 1992.
3. My position at Flamel Technologies, S.A. is Director of Research and Development in Oral Dosage Forms Department.
4. I have a Ph.D. in Polymer Chemistry.
5. I have worked in the area of pharmaceutical compositions for 23 years.
6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for delayed and controlled release of active principles.
7. I reviewed the office action mailed October 26, 2010 for U.S. Application No. 10/826,690.
8. I also reviewed Li *et al.* (US 2003/0035840), the reference cited by the Examiner in the 35 U.S.C. § 103(a) rejections.
9. I noted that Li, in example 1, is preparing coated pellets starting from inert cores with size of 30-35 mesh. It is straightforward to calculate the final diameter of the obtained coated pellets as follows:
10. The structure of the coated granules described in Li is depicted in figure 1 below. A thick layer containing the drug substance is deposited onto an inert core of diameter

R0 ("inert core"). This granule is covered by a coating that controls the release of the drug, leading to a coated granule of diameter R2

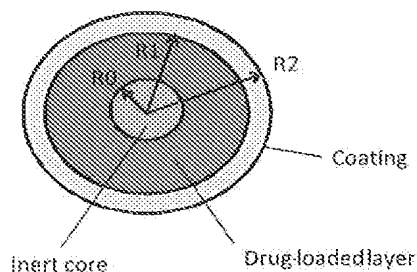


FIGURE 1

11. Below I calculated the diameter of the coated pellets of Li and showed that the diameters of the coated pellets are greater than the particle diameters claimed in this application.

12. The calculations are based on elementary geometric considerations justified by the spherical shape of the inert core (See Li paragraph at 0054) and from the data disclosed in the example 1 of Li.

13. To calculate the diameter of coated pellets according to Li, I first set the following variables:

- a.  $M_0$  is the mass (in kg) of the inert carrier with specific weight  $\rho_0$  (in  $\text{kg/m}^3$ )
- b.  $R_0$  is the radius of the inert carrier (in m)
- c.  $M_1$  is the mass of active plus additives deposited onto the inert carrier and  $\rho_1$  the specific mass (in  $\text{kg/m}^3$ ) of this drug loaded layer
- d.  $R_1$  is the radius of the drug containing granule (in m)
- e.  $M_2$  is the mass of coating with a specific weight  $\rho_2$  ( $\text{kg/m}^3$ ). and
- f.  $R_2$  is the radius of the coated granule (in m).

14. The number of beads was given by:

$$N = \frac{3M_0}{4\pi R_0^3 \rho_0} \quad (1)$$

15. The mass of drug per particle,  $m_1$ , and the mass of coating per particle,  $m_2$ , were given by:

$$m_1 = \frac{M_1}{N} \quad \text{and} \quad m_2 = \frac{M_2}{N} \quad (2)$$

16. From elementary geometry:

$$m_1 = \frac{4\pi}{3} \rho_1 [R_1^3 - R_0^3] \quad \text{and} \quad m_2 = \frac{4\pi}{3} \rho_2 [R_2^3 - R_1^3] \quad (3)$$

17. Finally the radius  $R_2$  of the particle was given by:

$$R_2 = \left[ R_0^3 + \frac{3m_1}{4\pi\rho_1} + \frac{3m_2}{4\pi\rho_2} \right]^{1/3} \quad (4)$$

where  $m_1$  and  $m_2$  were given by (1) and (2).

18. The specific weight of the sugar spheres was  $\rho_0 = 1580$  g/L (density = 1.58)<sup>1</sup>. The layer containing the drug substance was deposited by spray coating, and its specific weight  $\rho_1$  was assumed to be equal to 1200 g/liter (density = 1.2). Similarly, the specific weight of the coating  $\rho_2$  was assumed to be equal to 1000 g/liter (density = 1). Spray coating processes generally lead to porous layers, with low apparent density. However, the porosity has been neglected to calculate the minimum size of the coated granules disclosed by Li.

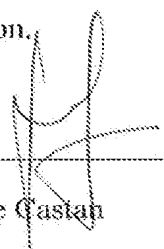
19. Table 1, below, shows the calculated diameter of the coated pellet for Li's Example 1. As a result the diameter in microns was 1000  $\mu\text{m}$ .

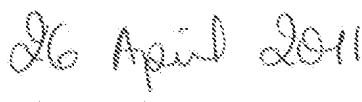
|                               |            |
|-------------------------------|------------|
| N° of example                 | 1          |
| <i>Neutral beads</i>          |            |
| M0 (Kg)                       | 1,06       |
| $\rho_0$ (kg/m <sup>3</sup> ) | 1580       |
| R0 ( m)                       | 0,00027375 |
| <i>Drug-loaded core</i>       |            |
| M1 (Kg)                       | 2,94       |
| $\rho_1$ (kg/m <sup>3</sup> ) | 1200       |
| <i>Coating</i>                |            |
| M2 (Kg)                       | 1          |
| $\rho_2$ (kg/m <sup>3</sup> ) | 1000       |
| R2 ( m)                       | 0,000501   |
| N° of example                 | 1          |
| Diameter( microns)            | 1000       |

Table 1

20. I declare that all statements made of my own knowledge are true and all statements made on information and belief are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or

imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.

  
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Catherine Castan

  
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Date

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<sup>3</sup> Cf. Handbook of Pharmaceutical Excipients, Fifth Edition, page 752